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Review of the neurophysiological responses to spinal manipulative therapy: Review protocol and narrative review

MASTERARBEIT

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Index

1. Abstract

Background/Objective: Spinal manipulative therapy (SMT) is one of the most widely used techniques in daily chiropractic practice worldwide. However, the underlying neurological mechanisms of SMT are not yet fully understood. For this reason, the Swiss Chiropractic Association (ChiroSuisse) is supporting a systematic review on the current state of evidence for the mechanisms underpinning the neurobiological effects of SMT.

Methods: First, a scoping review was conducted, leading to a protocol for a systematic literature review in the future. The literature search was performed with the help of a professional librarian and included seven databases: Medline, Pubmed, EMBASE, CINAHL, Cochrane, PEDro and Scopus for all the time to mid-february 2016. Second, the results of the research were briefly summarized and a first conclusion was defined.

Results: A total of 4001 potential relevant articles were identified through database searching. After duplicate removal, 2135 papers remained. Abstract screening allowed the exclusion of another 2084 papers. The remaining 51 papers were selected for this narrative review and were categorized into four subgroups: afferent nervous system (13 papers), efferent nervous system (7 papers), sympathetic and parasympathetic nervous system (22 papers) and H-reflex/T-reflex (11 papers) of which two papers were listed twice. For the afferent system, sensibility to thermal stimuli, brain activity, somatosensory evoked potentials, proprioception, repositioning sense and postural sway were categories included in the review. As for the efferent system, motor evoked potential studies were included. For the sympathetic and parasympathetic nervous system heart rate variability, blood pressure, pupil diameter, skin conductance and blood flow studies were included as well as blood concentrations of cortisol, neurotensin, oxytocin, epinephrine, norepinephrine, orexin A, β-endorphin and salivary amylase.

Conclusion: Many current research studies show a beneficial effect of SMT on pain intensity. However, the results of the present review suggest that this effect could be based on changes in the afferent nervous system, as all studies on brain activity and somatosensory evoked potentials after SMT reported relevant changes. The results of the effects of SMT on the efferent nervous system were inconclusive. SMT seems to affect the sympathetic nervous system changing peripheral blood flow while some studies demonstrated effects of SMT on blood levels of different hormones and on skin conductance. Effects on H-reflexes show attenuation. Future studies should focus on the dose response of SMT applied to single, well-defined spinal segments as well the long term effects on the nervous system.

2. List of abbreviations

CHEPS	Contact heat evoked potentials
EMG	Electromyography
LBP	Low back pain
MEP	Motor evoked potentials
MRI	Magnetic resonance imaging
PICO	Patient, intervention, comparison, outcome
SMT	Spinal manipulative therapy
SSEP	Somatosensory evoked potentials

3. Introduction

Multimodal care is currently the standard of care in chiropractic treatment, as patients are more likely to improve with more than one treatment modality (1). Nevertheless, spinal manipulative therapy (SMT) is one of the most widely used techniques in daily chiropractic practice worldwide (2). SMT is the application of a force to specific body tissues. Traditionally, it is done manually. Force, velocity, direction of load and location can vary. In this paper SMT describes high velocity, low amplitude force application to a vertebral joint (3). For acute low back pain (LBP), SMT has been proven to be more effective than a sham intervention for pain, physical function, overall-health and quality of life in the short-term (3 months) (4). There is also moderate evidence that functional improvement after SMT is still present after 6 months. Furthermore in combination with exercises, SMT is more beneficial than mobilisation plus exercise (5).

However, the underlying neurophysiological mechanisms of SMT are not yet fully understood (6). For this reason, the Swiss Chiropractors' Association (Chirosuisse) is supporting a systematic review on the current state of evidence for the mechanisms underpinning the neurobiological effects of SMT. As a first step, a scoping review was conducted.

3.1. Scoping review

In Pubmed, a scoping search for neurophysiological effects of SMT revealed multiple results related to the following areas of the nervous system:

Spinal cord level

Three studies were found that investigated spinal cord mechanisms. Fryer et al. used a randomised controlled crossover design study of 14 asymptomatic subjects (7). SMT was performed on L5/S1 bilaterally in the treatment group while the control group received 45 seconds of side posture lying without any contact on the spine. Motor evoked potentials (MEP), elicited by transcranial magnetic stimulation, H-reflexes (measured at N.tibialis posterior) and M-waves were measured pre- and post-intervention. H-reflexes represent activity at the spinal cord level, M-waves represent the activity at the muscular level and MEP represent the excitability of the motor cortex. SMT showed significant reduction in H-reflexes in comparison to the sham intervention. No significant changes in MEP latency were noted although a moderate reduction in excitability of the motor cortex was observed. Fryer concluded that SMT produces a reduction in spinal and corticospinal reflex excitability (7).

Dishman et al. investigated whether SMT to the cervical and lumbar spine could affect distal reflexes (8). In 36 subjects H-Reflex from the Nervus tibialis was measured before and after either cervical (C5/6) and/or lumbar (L5/S1) SMT. Significant transient motoneuronal

excitability suppression was measured for 60 seconds after SMT on the lumbar spine. No effect on N. tibialis could be measured by applying SMT to the cervical spine but a significant effect was observed following lumbar SMT. Thus, spinal HVLAT appears to only affect α-motoneurons at the level of treatment (8).

In 2001, Dishman et al. published another study (9) where 15 subjects were treated by either SMT of L5/S1 or massage or as a control group for comparison. The N.tibialis H-reflex was measured before and immediately after the intervention. Only after SMT a significant transient attenuation of α-motoneuronal excitability was elicited. The conclusion of this study was that SMT has a greater inhibitory effect on motoneuron excitability compared to massage or a control group (9).

Central nervous system and pain sensitivity

Four studies were found that investigated the effects of SMT on the telencephalon or the effects on pain sensitivity. As there are several pain centres involved, this topic will be discussed in the brain section.

Bishop et al. published a randomised experimental design study with 90 healthy patients in order to obtain information on regional pain modulation by SMT in the cervical or lumbar spine (10). Pressure and thermal pain sensitivity were measured before and after the SMT intervention. The pressure pain threshold (PPT) did not significantly change but a significant reduction in limb sensitivity was elicited. Regardless of the type of intervention, the reduction was larger for the lower extremity than for the upper extremity. Thermal stimuli sensation was significantly reduced by SMT compared to the control group and to the group that did specific exercises. Therefore, the results suggest that SMT has the potential for inhibiting the formation of central sensitization of pain (10).

Haavik and Murphy conducted a case control study to investigate immediate sensorimotor neurophysiological effects of SMT measured by somatosensory evoked potentials (SSEP) (11). 12 subjects with neck stiffnes and/or neck pain without acute symptoms at the time of the experiment were included and an additional 12 subjects took part in a passive head movement control intervention. N. medianus was stimulated and SSEP were recorded before and 30 minutes after the treatment. Decrease in the parietal and frontal lobe SSEP peak amplitudes but no change in latency following SMT was observed. Most changes in the frontal and parietal lobes lasted for 20 minutes. In the control group no significant amplitude change were observed. The conclusion of this study suggests that a change in somatosensory processing and sensorimotor integration through SMT may help to better understand the mechanisms for the relief of pain and rehabilitation of functional ability in neck pain patients (11).

In a randomised study design by Gay et al., 24 volunteers were given exercises to induce delayed onset muscular low back pain (12). Afterwards they were treated either by SMT, Spinal Mobilisation or Therapeutic Touch Control. Before and after treatment, functional magnetic resonance imaging (fMRI) was conducted to see which pain processing network areas were involved and which descending pain modulatory system pathways were activated before and after treatment. Subjects rated their low back pain on a 101 point numerical rating scale. Additionally, pressure pain thresholds were measured during the tests locally and at remote places with a dynamometer. No significant difference between the groups was noted for pain intensity and pain sensitivity (pressure pain threshold) measurements. A significant reduction in pain intensity was observed when exercise was included with manual therapy. No change was observed for pain sensitivity. In fMRI, different activation schemes were observed. The positive connection between the somatosensory cortex and the anterior insula increased in the right hemisphere following SMT and decreased following mobilisation. The functional connectivity between the somatosensory cortex and the periaqueductal grey increased in the right hemisphere following SMT and mobilisation and decreased following therapeutic touch control. The functional connectivity between the right anterior insula and the left posterior cingulate cortex increased following SMT and mobilisation and decreased following therapeutic touch control. In conclusion, these changes in functional connectivity between brain regions may be the underlying causes for the relief of pain (12).

Sympathetic and parasympathetic nervous system

Three studies were found that investigated the effects of SMT on the autonomic nervous system.

Budgell et al. conducted a controlled crossover trial with the aim of measuring the effects of SMT to the thoracic spine on heart rate variability (13). 28 volunteers were treated with SMT on the thoracic spine or with a sham intervention. Heart rate was measured five minutes before and after the treatment. In the SMT group, the rate significantly increased after the treatment, which was not observed in the sham intervention group. The authors concluded that there is a significant short-term increase in sympathetic output due to SMT (13).

Ward et al. studied possible effects of upper thoracic spine manipulation on cardiovascular response (14). In a single-blind, randomised controlled trial 36 subjects were treated either with SMT at the level of the first to fourth thoracic vertebra (T1-T4), activator-based placebo manipulation or a no-T-spine contact control (contact elsewhere, not at the thoracic spine). Electrocardiogram, bilateral pulse oximetry and blood pressure measurements were taken. Significant differences or changes were found neither between the groups nor within the groups. The conclusion was that SMT at the above mentioned levels does not affect cardiovascular physiologic responses in young normotensive individuals (14).

Kingston et al. (15) investigated the effect of mobilization compared to placebo or control and its direction of change in a systematic review. In conclusion they found a sympatho-excitatory effect, not related to the level treated (15).

3.2. Aims of the study

Based on the scoping review, a systematic literature research was performed on the response of the nervous system to SMT.

The aim of this thesis was: (1) to develop the protocol for a systematic review on the responses of the nervous system to SMT containing inclusion and exclusion criteria for the literature research and criteria for the quality assessment, (2) to give a narrative overview of the selected articles and (3) to identify promising areas for future research studies. The hypothesis is that SMT has its main effects on the autonomous nervous system.

4. Material und Methods

4.1. Setting

A systematic literature research was performed by a professional librarian. Databases used were Medline, Pubmed, EMBASE, CINAHL, Cochrane, PEDro and Scopus.

4.2. Keywords

Patient, intervention, comparison and outcome (PICO) form the PICO criteria that were used to develop the literature search strategy.

Table 1: Keywords are structured according to the PICO framework.

Patient	**Intervention**	**Comparison**	**Outcome**
Humans Not animals Subjects	Back Cervical spine C0/C1 High velocity low amplitude treatment Lumbar spine Neck Sacrum Spinal manipulation Spine S5/Coccyx Thoracic spine Type V mobilisation	Any other treatment than SMT, sham intervention or no intervention	Afferent Body temperature Brain Efferent Golgi tendon organ Heart rate Hormones Muscle spindle Nervous system Neuroendocrine Neurophysiologic* Parasympathetic nervous system Sympathetic nervous system Thermal sensitivity

4.3. Study Selection

After removing duplicate citations, two reviewers determined which articles should be included in the systematic review by scanning the titles, abstracts and keywords on the basis of the inclusion and exclusion criteria. For the remaining articles, full-text versions were obtained.

4.4. Inclusion/Exclusion criteria

Inclusion criteria:

- English language
- German language
- Adults (>18 years)
- Intervention is SMT to the spine
- Effects to any part of the nervous system were investigated, namely: central nervous system, peripheral nervous system, sympathetic nervous system, neuroendocrine system, proprioception

Exclusion criteria:

- Children/adolescents (<18 years)
- Studies in languages other than English or German
- Techniques other than HVLAT were applied, e.g. mobilisation, massage
- Other effects studied
    - Electromyography EMG
    - Immune system
    - Infantile Colic
    - Pressure Pain Threshold

4.5. Assessment of data quality

Table 2: Checklist for quality review of general papers (12), purpose-adjusted.

	Criteria	Score (Yes = 1, No = 0, Unable to determine = 0)
Reporting		
1	Is the hypothesis/aim/objective of the study clearly described?	Yes / No
2	Are the main outcomes to be measured clearly described in the Introduction or Methods section? *If the main outcomes are first mentioned in the Results section, the question should be answered no.*	Yes / No
3	Are the characteristics of the patients included in the study clearly described? *In cohort studies and trials, inclusion and/or exclusion criteria should be given. In case-control studies, a case-definition and the source for controls should be given.*	Yes / No
4	Are the interventions of interest clearly described? *Treatments and placebo (where relevant) that are to be compared should be clearly described.*	Yes / No

5	Are the distributions of principal confounders in each group of subjects to be compared clearly described? *A list of principal confounders is provided.*	Yes / No
6	Are the main findings of the study clearly described? *Simple outcome data (including denominators and numerators) should be reported for all major findings so that the reader can check the major analyses and conclusions. (This question does not cover statistical tests which are considered below.)*	Yes / No
7	Does the study provide estimates of the random variability in the data for the main outcomes? *In non-normally distributed data the inter-quartile range of results should be reported. In normally distributed data the standard error, standard deviation or confidence intervals should be reported. If the distribution of the data is not described, it must be assumed that the estimates used were appropriate and the question should be answered yes.*	Yes / No
8	Have all important adverse events that may be a consequence of the intervention been reported? *This should be answered yes if the study demonstrates that there was a comprehensive attempt to measure adverse events. (A list of possible adverse events is provided).*	Yes / No
9	Have the characteristics of patients lost to follow-up been described? *This should be answered yes where there were no losses to follow-up or where losses to follow-up were so small that findings would be una V ected by their inclusion. This should be answered no, where a study does not report the number of patients lost to follow-up.*	Yes / No
10	Have actual probability values been reported (e.g.0.035 rather than <0.05) for the main outcomes except where the probability value is less than 0.001?	Yes / No
External validity		
11	Were the subjects asked to participate in the study representative of the entire population from which they were recruited? *The study must identify the source population for patients and describe how the patients were selected. Patients would be representative if they comprised the entire source population, an unselected sample of consecutive patients, or a random sample. Random sampling is only feasible where a list of all members of the relevant.*	Yes / No / Unable to determine
12	Were those subjects who were prepared to participate representative of the entire population from which they were recruited? *The proportion of those asked who agreed should be stated. Validation that the sample was representative would include demonstrating that the distribution of the main confounding factors was the same in the study sample and the source population.*	Yes / No / Unable to determine
Internal validity – bias		
14	Was an attempt made to blind study subjects to the intervention they have received? *For studies where the patients would have no way of knowing which intervention they received, this should be answered yes.*	Yes / No / Unable to determine
15	Was an attempt made to blind those measuring the main outcomes of the intervention?	Yes / No / Unable to determine
16	If any of the results of the study were based on “data dredging”, was this made clear? *Any analyses that had not been planned at the outset of the study should be clearly indicated. If no retrospective unplanned subgroup analyses were reported, then answer yes.*	Yes / No / Unable to determine
17	In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients, or in case-control studies, is the time period between the intervention and outcome the same for cases and controls? *Where follow-up was the same for all study patients the answer should yes. If different lengths of follow-up were adjusted for by, for example, survival analysis the answer should be yes. Studies where differences in follow-up are ignored should be answered no.*	Yes / No / Unable to determine

18	Were the statistical tests used to assess the main outcomes appropriate? *The statistical techniques used must be appropriate to the data. For example non-parametric methods should be used for small sample sizes. Where little statistical analysis has been undertaken but where there is no evidence of bias, the question should be answered yes. If the distribution of the data (normal or not) is not described it must be assumed that the estimates used were appropriate and the question should be answered yes.*	Yes / No / Unable to determine
19	Was compliance with the intervention/s reliable? *Where there was non-compliance with the allocated treatment or where there was contamination of one group, the question should be answered no. For studies where the effect of any misclassification was likely to bias any association to the null, the question should be answered yes.*	Yes / No / Unable to determine
20	Were the main outcome measures used accurate (valid and reliable)? *For studies where the outcome measures are clearly described, the question should be answered yes. For studies which refer to other work or that demonstrates the outcome measures are accurate, the question should be answered as yes.*	Yes / No / Unable to determine
Internal validity – confounding (selection bias)		
21	Were the patients in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited from the same population? *For example, patients for all comparison groups should be selected from the same hospital. The question should be answered unable to determine for cohort and case-control studies where there is no information concerning the source of patients included in the study.*	Yes / No / Unable to determine
22	Were study subjects in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited over the same period of time? For a study which does not specify the time period over which patients were recruited, the question should be answered as unable to determine.	Yes / No / Unable to determine
23	Were study subjects randomised to intervention groups? *Studies which state that subjects were randomised should be answered yes except where method of randomisation would not ensure random allocation. For example alternate allocation would score no because it is predictable.*	Yes / No / Unable to determine
26	Were losses of patients to follow-up taken into account? *If the numbers of patients lost to follow-up are not reported, the question should be answered as unable to determine. If the proportion lost to follow-up was too small to affect the main findings, the question should be answered yes.*	Yes / No / Unable to determine
Power		
27	Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%? Sample sizes have been calculated to detect a difference of x% and y%.	Yes / No

A maximum total score of 24 points can be given as follows: 10 points are given for reporting issues, 2 point for evaluating external validity (i.e. whether the study is representative for the population), 7 points are given for internal validity matters concerning bias such as faults with blinding and adjusting data to compare them and 4 points for finding selection bias. Finally, the power is rated with a total of 1 point.

4.6. Data extraction

- Study design
- Patient characteristics (number, age, gender)
- Intervention: level of manipulation applied
- Control: was there a control treatment? If so, which one?
- Outcome:
    - Which neurophysiologic outcome parameters were measured?
    - What effects on the outcome measures were found?

5. Results

5.1. Literature selection

4001 papers were identified through database searching (Fig. 1). After duplicate removal, 2135 papers remained. Abstract screening for inclusion and exclusion criteria allowed the exclusion of another 2084 papers. The remaining 51 papers were selected for this narrative review and were categorized into four subgroups according to the part of the nervous system that they focused on. For the afferent system sensibility to thermal stimuli, brain activity, SSEP, proprioception, repositioning sense and postural sway were included. For the efferent system MEP were included. For the sympathetic and parasympathetic nervous system heart rate variability, blood pressure, pupil diameter, skin conductance and blood flow were included as well as blood concentrations of cortisol, neurotensin, oxytocin, epinephrine, norepinephrine, orexin A, β-endorphin and salivary amylase. Furthermore H- and T-reflexes studies were used. Two studies are listed twice. Namely the one of Fryer et al. (7), that is listed in the efferent and the H-Reflex section and the study of Ogura et al. (16), that is listed in the afferent and the sympathetic/parasympathetic section.

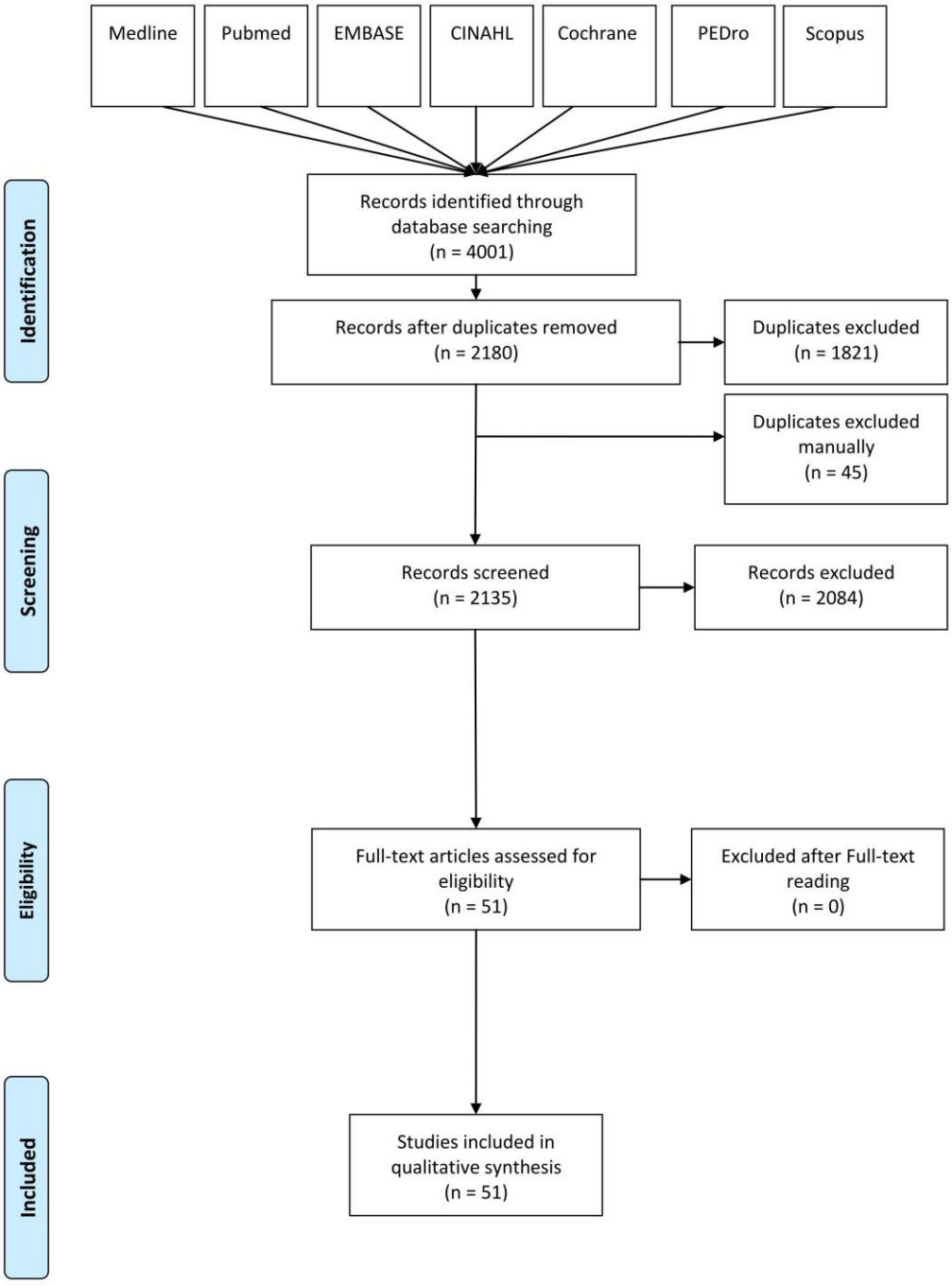

Figure 1: Procedure for the study selection with databases used for the literature search.

5.2. Overview of the selected papers

Afferent nervous system (13 papers)

Table 3: Overview on the papers to the afferent nervous system

Article	Participant characteristics	Design	Intervention	Control	Neurophysiologic outcome parameters	Other outcome parameters	Main outcome
Bishop, M. D., et al. (2011). Immediate reduction in temporal sensory summation after thoracic spinal manipulation. (10)	N = 90 Healthy volunteers, no neck or upper extremity pain in the last sixty days Mean age: 22.9 ± 2.7 years	Randomised experimental design	Postero-anterior cervicothoracic SMT	Specific cervical exercise or Rest	Pain reporting to thermal stimuli: first pain (pressure or A-delta mediated thermal pain responses),	Experimental pain sensitivity in cervical and lumbar innervated areas, pressure pain threshold, second pain, increase in the second pain intensity (also known as temporal sensory summation) Psychological questionnaires	No effect for pressure or A-delta mediated thermal pain responses. Thoracic SMT reduces temporal sensory summation in healthy subjects. Duration unknown, possible changes in the nociceptive afferent system caudal to the region of SMT.
Carrick, F. R. (1997). Changes in brain function after manipulation of the cervical spine. (17)	N = 500 Adult volunteers (health status unknown) Age: ≥ 18 years	Double-blind controlled study	SMT of the second cervical motion segment	No control. Pre-post comparison of intervention group	Brain activity visible on cortical maps measured before and after intervention.		Cervical SMT activates specific neurological pathways. Contralateral cortical activity increases following cervical SMT applied ipsilateral to an enlarged cortical map and decreases on the side opposite to SMT application.
Fisher, A. R., et al. (2015). The effect of cervical spine manipulation on postural sway in patients with nonspecific neck pain. (18)	N = 10 Patients with neck pain history of at least 4 weeks Mean age: 37.2	Randomised crossover study	Single SMT to a dysfunctional cervical segment	Passive head-movement	Centre of pressure deviation to know postural sway	Numeric rating scale for pain	No change in postural sway after a single cervical SMT

Article	Participant characteristics	Design	Intervention	Control	Neurophysiologic outcome parameters	Other outcome parameters	Main outcome
Gay, C. W., et al. (2014). Immediate changes after manual therapy in resting-state functional connectivity as measured by functional magnetic resonance imaging in participants with induced low back pain. (12)	N = 24 Painfree volunteers Mean age: 21.6 ± 4.2 years	Randomised study design with blinded assessment	Exercises to induce LBP followed by Lumbar SMT	Exercises to induce LBP followed by Spinal mobilization or Therapeutic touch	Changes in functional connectivity between brain regions.	Reduction in pain intensity on a numeric rating scale Pressure pain sensitivity changes measured with a dynamometer	Functional connectivity between brain regions are affected by SMT, mobilization and therapeutic touch. Pain intensity decreased after all interventions, without any difference between the groups. No changes in pain sensitivity between the groups.
Goertz, C. M., et al. (2016). Effects of spinal manipulation on sensorimotor function in low back pain patients - A randomised controlled trial. (19)	N = 221 LBP ≥ 4 (NRS 1-10) or ≥ 2 Age: 21-65 years	Three-arm randomised controlled trial	Lumbar, sacral and pelvic SMT (four treatments over two weeks)	Low-velocity variable amplitude or sham	Postural sway	Response to sudden load	No change in sensorimotor functions following SMT. Increase in medial to lateral excursion following Low-velocity variable amplitude treatment.
Haavik-Taylor, H. and B. Murphy (2007). Cervical spine manipulation alters sensorimotor integration: a somatosensory evoked potential study. (11)	N = 24 History of reoccurring neck stiffness and/or neck pain, without acute symptoms Mean age: 29.9 years	Pseudo-randomised case-control study	Single session of cervical SMT	Passive head movement	SSEP of N. medianus stimulation, measured at spinal, brainstem and cortical levels		Decrease in SSEP amplitude for the intervention group at frontal and parietal measurements. Changes lasted 20 minutes on average. No changes in the control group.

Article	Participant characteristics	Design	Intervention	Control	Neurophysiologic outcome parameters	Other outcome parameters	Main outcome
Haavik Taylor, H. and B. Murphy (2010). The effects of spinal manipulation on central integration of dual somatosensory input observed after motor training: a crossover study. (20)	N = 11 Patients with a self-reported history of reoccurring neck pain or stiffness Mean age: 28.9 ± 6 years	Time-series design with reversal	Cervical SMT followed by a motor training task	no intervention followed by a motor training task	SSEP ratios before and after stimulation of N.medianus and N.ulnaris.		An increase of the ratio of simultaneous median and ulnar stimulation to the sum of individual stimulation of the nerves resulted for the control group and a decrease of this ratio was observed for the intervention group. Cervical SMT changes cortical integration of dual somatosensory input. Cervical SMT changes the response of the central nervous system to succeeding motor training tasks.
Learman, K. E., et al. (2009). Effects of spinal manipulation on trunk proprioception in subjects with chronic low back pain during symptom remission. (21)	N = 33 Chronic LBP Age: 24-54 years	Unbalanced randomised controlled crossover study	Lumbar SMT in sideposture	Sham procedure: in sideposture, manual contact on thoracolumbar junction to shield the lumbar spine from movement. Held into torqued position for 15 seconds.	Trunk proprioception: - Joint position sense - Threshold to detect passive motion - Direction of motion - Force reproduction		Joint position sense was changed following SMT. Joint position sense was not changed following the sham intervention. Effects in both, the intervention and the control group measured as a threshold to detect passive motion. No change for the direction of motion could be measured.

Article	Participant characteristics	Design	Intervention	Control	Neurophysiologic outcome parameters	Other outcome parameters	Main outcome
Ogura, T., et al. (2011). Cerebral metabolic changes in men after chiropractic spinal manipulation for neck pain. (16)	N = 12 Male volunteers with cervical pain and shoulder stiffness Mean age: 28±7 years	One group pretest-posttest	SMT, application site not defined	No control. Pre to post comparison of intervention group.	18F-Fluorodeoxyglucose Positron emission tomography FDG-PET	Visual analogue scale Muscle tone Salivary amylase	SMT increased activity in inferior prefrontal cortex, anterior cingulated cortex and middle temporal gyrus. SMT decreased activity in cerebellar vermis and visual association cortex.
Rogers, R. G. (1997). The effects of spinal manipulation on cervical kinesthesia in patients with chronic neck pain: a pilot study. (22)	N = 20 Chronic neck pain (≥4 months) Age: -	Matched, non-randomised controlled trial	Six sessions of SMT to the cervical and upper thoracic regions during a 3-4 week period	Stretching exercises for the cervicothoracic muscles	Proprioception acuity (head repositioning)	Visual analogue scale for pain	Significant improvement of head repositioning sense in subjects with chronic neck pain following SMT.
Sparks, C., et al. (2013). Using functional magnetic resonance imaging to determine if cerebral hemodynamic responses to pain change following thoracic spine thrust manipulation in healthy individuals. (23)	N = 10 Healthy volunteers Mean age: 31.2 years	One group pretest-posttest	Midthoracic SMT	No control group. Pre-to postthrust comparison. All participants first received a five minute set of noxious stimuli applied to the index finger with intermittent pauses. During that time, fMRI was taken. The same procedure was done post intervention.	Blood oxygenation level dependent functional magnetic resonance imaging fMRI (cerebral blood flow)	Numeric rating scale for pain	Following SMT, a decrease in pain perception and a decrease in insular cortex blood flow was observed.

Article	Participant characteristics	Design	Intervention	Control	Neurophysiologic outcome parameters	Other outcome parameters	Main outcome
Taylor, H. H. and B. Murphy (2010). Altered central integration of dual somatosensory input after cervical spine manipulation. (24)	N = 13 History of reoccurring neck stiffness and/or neck pain without acute symptoms Mean age: 28 ±6.3 years	Randomised crossover design	cervical SMT	Passive head movement	SSEP ratios after N.medianus and N.ulnaris stimulation		A decrease in the ratio of simultaneous median and ulnar stimulation to the sum of individual stimulation of the nerves for the cortical component was observed after cervical SMT at the frontal measurement. No changes after the control intervention.
Yang, J., et al. (2015). Changes in proprioception and pain in patients with neck pain after upper thoracic manipulation. (25)	N = 30 Workers with mechanical neck pain Mean age intervention group: 30.8 years; control group: 28.07 years	Randomised controlled trial	Upper thoracic SMT after cervical stability training. Three sessions of 30 minutes a week over six weeks.	Cervical stability training. Three sessions of 30 minutes a week over six weeks.	Electrogoniometer to measure reposition sense/proprioception	Visual analogue scale for pain	Significantly reduced repositioning errors and greater reduction in pain in the SMT group than the control group. Significant differences in proprioception were observed for both intervention groups (direction of change was not reported).

Efferent nervous system (7 papers)

Table 4: Overview on the papers to the efferent nervous system

Article	**Participant characteristics**	**Design**	**Intervention**	**Control**	**Neurophysiologic outcome parameters**	**Other outcome parameters**	**Main outcome**
Clark, B. C., et al. (2011). Neurophysiologic effects of spinal manipulation in patients with chronic low back pain. (26)	N = 20: 10 chronic LBP 10 asymptomatic controls Age: 23.7±6.1 years and 22.9±1.9 years	Non-randomised controlled trial	Lumbar SMT	Measurements before and after the intervention/pre-post comparison. Symptomatic and asymptomatic patients.	Transcranial magnetic stimulation measures as MEP at M. erector spinae	Audible joint sound caused by SMT yes/no, M. erector spinae stretch reflex amplitude induced by electromechanical tapping that triggers short-latency stretch reflexes.	Single SMT does not alter MEP neither in patients with nor in patients without chronic LBP.
Daligadu, J., et al. (2013). Alterations in cortical and cerebellar motor processing in subclinical neck pain patients following spinal manipulation. (27)	N = 20: 10 with subclinical neck pain 10 asymptomatic controls Mean age: 23.8 years	Non-randomised controlled trial	Cervical SMT	The same intervention with asymptomatic patients Measurements before and after the intervention/pre-post comparison.	Transcranial magnetic stimulation and MEP of the right M.interosseus dorsalis	Motor sequence task performance for mean reaction time. Combined interventions with motor sequence learning.	Cervical SMT applied to patients with neck pain can normalize cerebellar inhibition.
Dishman, J. D., et al. (2002). First Prize: Central motor excitability changes after spinal manipulation: a transcranial magnetic stimulation study. (28)	N = 24 Healthy volunteers Age: -	Counterbalanced controlled trial	Homolateral L5/S1 SMT	Side posture positioning without any manipulative thrust	Transcranial MEP (10 times) measured at the right M.gastrocnemius and peak-to-peak amplitudes before and after intervention (0', 5', 10')		Significant central motor/MEP amplitude facilitation occurs 20-60s after SMT. No change in the control group.

Article	Participant characteristics	Design	Intervention	Control	Neurophysiologic outcome parameters	Other outcome parameters	Main outcome
Dishman, J. D., et al. (2008). Motor-evoked potentials recorded from lumbar erector spinae muscles: a study of corticospinal excitability changes associated with spinal manipulation. (29)	N = 72 Asymptomatic subjects Age: 20-40 years	Randomised controlled trial	L5/S1 SMT	L5/S1 prethrust positioning to the end point range of motion by low-velocity zygaphyseal joint loading Or side-lying position for the same time	MEP of M.erector spinae pre- and postintervention		Transient increase of MEP following SMT, meaning postsynaptic facilitation of α-motoneurons or corticomotoneurons. No change in MEP following control interventions.
Fryer, G. and A. J. Pearce (2012). The effect of lumbosacral manipulation on corticospinal and spinal reflex excitability on asymptomatic participants. (7)	N = 14 asymptomatic volunteers Mean age: 23±5.4 years	Randomised, controlled crossover design	L5/S1 SMT bilaterally	Lateral recumbent position for 45 s without truncal torque or manual contact	Motor-evoked potential (MEP)	MEP/M-wave ratio H-reflex of M. gastrocnemius via N.tibialis	Significant decrease in motor neuron excitability following bilateral L5/S1 SMT was measured. MEP latency changes were not significant. Only small changes in the control group.
Haavik-Taylor, H. and Murphy B. (2007). Transient modulation of intracortical inhibition following spinal manipulation. (30)	N = 13 History of recurring neck stiffness and/or neck pain without acute symptoms Age: -	Time-series design with reversal	Dysfunctional cervical joint SMT	Passive head movement control condition Control group with no intervention	MEP and cortical silent periods (CSP) in M. abductor pollicis brevis		Decrease in cortical silent period in the M.abductor pollicis brevis in the SMT group. No significant decreases in the control groups.

Article	Participant characteristics	Design	Intervention	Control	Neurophysiologic outcome parameters	Other outcome parameters	Main outcome
Taylor, H. and Murphy, B. (2008). Altered sensorimotor integration with cervical spine manipulation. (31)	N = 12 History of reoccurring neck pain Age: 27.1±7.7 years	Time-series design with reversal	Cervical SMT of dysfunctional joints	Passive head movement	From M. abductor pollicis brevis and M. extensor indicis: MEP	From M. abductor pollicis brevis and M. extensor indicis: Short interval intracortical inhibition, short interval intracortical facilitation (SICF), Cortical silent periods, F-waves after N. medianus stimulation	For the M. abductor pollicis brevis, cervical SMT caused a decrease in short interval intracortical inhibition, an increase in SICF and a decrease in the length of the cortical silent period. For the M.extensor indicis, a decrease in SICF and an increase of the length of the cortical silent period was measured. MEP and F-waves did not change significantly. No changes after the control intervention.

Sympathetic and parasympathetic nervous system (22 papers)

Table 5: Overview on the papers to the sympathetic and parasympathetic nervous system

Article	**Participant characteristics**	**Design**	**Intervention**	**Control**	**Neurophysiologic outcome parameters**	**Other outcome parameters**	**Main outcome**
Budgell, B. and B. Polus (2006). The Effects of Thoracic Manipulation on Heart Rate Variability: A Controlled Crossover Trial. (13)	N = 28 normotensive, healthy adults Mean age: 29±7 years	Controlled cross over trial	Upper thoracic SMT	Sham thrust over the scapulae bilaterally	Changes in heart-rate variability	Visual analogue scale	Low frequency components increased following SMT, normalized high frequency components decreased. No changes resulted from the control procedure.
Desmarais, A., et al. (2011). Tuning the gain of somato-sympathetic reflexes by stimulation of the thoracic spine in humans. (32)	N= 17 healthy volunteers Mean age: 25±1.1 years	Counterbalanced design	Phasic electrical stimulation of N.surae plus 3. SMT Th3-Th5 4. SMT to Th3-Th5 and Noxious heat	1. Phasic electrical stimulation of N.surae without heat or SMT 2. Tonic noxious heat applied to the skin over Th3-Th5	Skin conductance response amplitude and amplification by tonic noxious heat palmar and plantar.	Numeric rating scale, pain related anxiety rating scale, respiration frequency	No significant change during the control intervention. SMT decreased the amplitude of skin conductance response measured palmar, no significant change in the plantar measurement.
Giles, P. D., et al. (2013). Suboccipital decompression enhances heart rate variability indices of cardiac control in healthy subjects. (33)	N = 19 Healthy subjects Mean age: 25±2 years	Randomised cross over study	Upper cervical manipulative treatment	Sham manipulation or Time control	Electrocardiogram for resting heart rate and heart rate variability		Increase in high frequency measurements following SMT, meaning an enhancement of the parasympathetic control. No difference following the control interventions.

Article	Participant characteristics	Design	Intervention	Control	Neurophysiologic outcome parameters	Other outcome parameters	Main outcome
Harris, W. and R. J. Wagnon (1987). The effects of chiropractic adjustments on distal skin temperature. (34)	N = 196 Age: -	One group pretest-posttest	SMT C1-7 or T1-L3 or L4/L5	No control. Pre-post comparison of intervention group.	Changes in distal skin temperatures (fingertip)		Temperature increase after SMT of C1-7 or L4-5. Temperature decrease after SMT of T1-L3.
Knutson, G. A. (2001). Significant changes in systolic blood pressure post vectored upper cervical adjustment vs resting control groups: a possible effect of the cervicosympathetic and/or pressor reflex. (35)	<u>Experiment 1:</u> N = 80 Established patients 40 with signs of upper cervical subluxation/joint dysfunction, 40 without such signs Age: 21-83 years <u>Experiment 2:</u> N = 30 Established patients with signs of upper cervical subluxation/joint dysfunction Age: 14-83 years	Non-randomised, controlled clinical trial	Upper cervical SMT	Similarly positioned resting Experiment 1: patients without dysfunction Experiment 2: pre-post comparison	Blood pressure, pulse rate		Experiment 1: Upper cervical SMT causes significant decrease in systolic blood pressure in patients with dysfunctions in this area, not in the control group. Experiment 2: Significant decrease of the systolic blood pressure after SMT was observed.
McKnight, M. E. and DeBoer K. F. (1988). Preliminary study of blood pressure changes in normotensive subjects undergoing chiropractic care. (36)	N = 75 Group 1: with manipulable cervical dysfunctions at that day Group 2: without cervical dysfunctions Age: 20-35 years	Non-randomised controlled clinical trial	Group 1: SMT of the cervical spine	Group 2: motion palpation	Blood pressure		Cervical SMT causes a small decrease in the mean blood pressure. Significant decrease of systolic and diastolic blood pressures after SMT was observed.

Article	Participant characteristics	Design	Intervention	Control	Neurophysiologic outcome parameters	Other outcome parameters	Main outcome
Mohammadian, P., et al. (2004). Areas of capsaicin-induced secondary hyperalgesia and allodynia are reduced by a single chiropractic adjustment: a preliminary study. (37)	N = 20 Healthy subjects Mean age: 27 years	Randomised cross-over	Thoracic SMT to dysfunctional joints after capsaicin cream application to the forearm unilaterally.	Nonspinal manipulation treatment after capsaicin cream application to the forearm unilaterally. Additional pre-post comparison.	Blood flow	Mechanical hyperalgesia, stroking allodynia, spontaneous pain	Single SMT did not affect local blood flow.
Morgan, J. P., et al. (1985). A controlled trial of spinal manipulation in the management of hypertension. (38)	N = 29 Hypertensive blood pressure Mean age per group: 50.2±3.9 years and 48±3.2 years	Cross over study	6 times C0/C1 SMT, T1/T5 SMT, T11/L1 SMT	6 times sham manipulation: Soft tissue massage of T6/T10, L4-Sacrum	blood pressure		None of the treatments can reduce or control elevated systemic blood pressure.
Ogura, T., et al. (2011). Cerebral metabolic changes in men after chiropractic spinal manipulation for neck pain. (16)	N = 12 Male volunteers with cervical pain and shoulder stiffness Mean age: 28±7 years	One group pretest-posttest	SMT, application site not defined	No control. Pre to post comparison of intervention group.	Salivary amylase concentration in the blood	Visual analogue scale, muscle tone, 18F-Fluorodeoxyglucose Positron emission tomography FDG-PET	SMT decreased salivary amylase.

Article	Participant characteristics	Design	Intervention	Control	Neurophysiologic outcome parameters	Other outcome parameters	Main outcome
Padayachy, K., et al. (2010). The immediate effect of low back manipulation on serum cortisol levels in adult males with mechanical low back pain. (39)	N = 30 Acute mechanical LBP (≤4 weeks) Age: 18-35 years	Time-series design	"Low back" SMT	No control. Pre-post comparison of intervention group.	Daytime serum cortisol levels. Group A: Cortisol measured once before SMT and 5' after SMT Group B: Cortisol measured 5' before SMT, immediately before and 5' after SMT		The rate of change of daytime serum cortisol levels was increased following SMT. Decrease in serum cortisol levels following a short rest interval.
Perry, J., et al. (2011). A preliminary investigation into the magnitude of effect of lumbar extension exercises and a segmental rotatory manipulation on sympathetic nervous system activity. (40)	N = 50 Healthy patients Mean age: Intervention group 37.7±8.28 years Control group 36.9±8.27 years	Quasi-experimental, independent group's design	L4/5 Segmental rotational SMT	McKenzie's lumbar extension exercises	Skin conductance		Both treatments increased skin conductance during the intervention (sympathoexcitatory effect). Greater effect following SMT. No difference between the opening and the closing side in the SMT group.
Perry, J., et al. (2015). A randomised, independent groups study investigating the sympathetic nervous system responses to two manual therapy treatments in patients with LBP. (41)	N = 50 LBP of less than 12 weeks duration Age: 18-55 years	Randomised, independent group's design	Lumbar SMT on symptomatic segment	McKenzie's lumbar extension exercises	Skin conductance		Sympatho-excitatory responses during both interventions. SMT caused an increase of 255% in skin conductance, the control intervention a 94% increase.

Article	Participant characteristics	Design	Intervention	Control	Neurophysiologic outcome parameters	Other outcome parameters	Main outcome
Plaza-Manzano, G., et al. (2014). Changes in biochemical markers of pain perception and stress response after spinal manipulation. (42)	N = 30 Asymptomatic subjects Age: -	Single- blind randomised controlled study	SMT cervical SMT thoracic	Non-manipulation control	Blood levels of : Neurotensin Oxytocin Orexin A Cortisol		Significant increase in blood levels of neurotensin and oxytocin after cervical and thoracic SMT. Significant increase of cortisol concentration following cervical SMT. No change for Orexin A levels. The effects were transient and absent after two hours.
Puhl, A. A. and H. S. Injeyan (2012). Short-term effects of manipulation to the upper thoracic spine of asymptomatic subjects on plasma concentrations of epinephrine and norepinephrine-a randomized and controlled observational study. (43)	N = 36 Asymptomatic subjects Mean age intervention group: 26.4±1.1 years; control group: 25.9±1 years	Randomised controlled trial	SMT T1-T6 to a hypomobile segment	Sham intervention: same positioning as intervention group, without thrust.	Norepinephrine and epinephrine plasma concentrations		No effect on plasma concentrations of norepinephrine or epinephrine

Article	Participant characteristics	Design	Intervention	Control	Neurophysiologic outcome parameters	Other outcome parameters	Main outcome
Roy, R. A., et al. (2009). Heart rate variability modulation after manipulation in pain-free patients vs patients in pain. (44)	N = 51 1. Painless (33) 2. Acute low back pain (20) Age: Control: 37.4±10.7 years Sham (1): 33.28±9.2 years Treatment (1): 25.1±4 years Sham (2): 44.7±9.8 years Treatment (2): 35.7±11.7 years	Randomised controlled trial	Treatment group 1: Activator IV-assisted L5 manipulation Treatment group 2: SMT L5	Control group: prone, no intervention. Sham group 1: sham intervention with Activator IV instrument. Sham group 2: side posture with 5 seconds pressure without thrust.	Heart rate variability		The high frequency variable decreased except in the control groups, representing parasympathetic activity. The low frequency decreased except for the sham intervention in the pain-free group, representing sympathetic activity. Prevalence of high frequency over low frequency values was observed, representing a shift towards parasympathetic predominance.
Sillevis, R., et al. (2010). Immediate effects of a thoracic spine thrust manipulation on the autonomic nervous system: a randomized clinical trial. (45)	N= 100 Subjects with chronic cervical pain Age: 18-65 years	Randomised controlled trial	T3/T4 SMT	Placebo intervention	Pupil diameter, pupil diameter changes over time	Change in pain perception	No significant change in mean pupil diameter for the SMT group. However, there was a slight increase observed. No immediate change in pain perception.

Article	Participant characteristics	Design	Intervention	Control	Neurophysiologic outcome parameters	Other outcome parameters	Main outcome
Vernon, H. T., et al. (1986). Spinal manipulation and beta-endorphin: a controlled study of the effect of a spinal manipulation on plasma beta-endorphin levels in normal males. (46)	N= 27 Healthy men without back pain since 6 months Mean age: 23.1±2.9 years	Randomised controlled trial	20 min rest, then assessment of the upper cervical spine with joint play manoeuvres, maximal unidirectional rotation of head and neck with cervical SMT	Sham-group: 20 min rest, then assessment of the upper cervical spine with joint play manoeuvres, maximal unidirectional rotation of head and neck with oscillatory pressure into the elastic barrier on one segment. And Control-group: 20 min rest	Beta-endorphin levels		Increase in serum beta-endorphin levels in the SMT group 5 minutes postintervention. Decrease of those levels in the sham and control groups.
Ward, J., et al. (2013). Immediate effects of anterior upper thoracic spine manipulation on cardiovascular response. (14)	N = 36 Normotensive participants Mean age: 26.8±4.6 years	Randomised, single-blind controlled trial	T1-T4 SMT	Activator-based placebo manipulation Or No T-spine contact	Electrocardiogram, bilateral pulse oximetry, bilateral blood pressure measurement		No significant change.
Ward, J., et al. (2015). Immediate effects of upper thoracic spine manipulation on hypertensive individuals. (47)	N= 50 Hypertensive participants Mean age: 45.5±13.9 years	Randomised, single-blind controlled trial	Posterior to anterior T1-T4 SMT	No T-spine contact	Electrocardiogram, bilateral pulse oximetry, bilateral blood pressure measurement		No significant changes in cardiovascular physiologic responses by upper thoracic SMT in hypertensive individuals, at least in short-term.

Article	Participant characteristics	Design	Intervention	Control	Neurophysiologic outcome parameters	Other outcome parameters	Main outcome
Welch, A. and R. Boone (2008). Sympathetic and parasympathetic responses to specific diversified adjustments to chiropractic vertebral subluxations of the cervical and thoracic spine. (48)	N = 40 Normal blood pressure, no history of heart disease, asymptomatic Age: 25-55 years	One group pretest posttest	Cervical SMT or Thoracic SMT	No control. Pre-post comparison of intervention group.	Diastolic blood pressure and pulse rate, heart rate variability in 7 patients		Decrease in diastolic blood pressure after cervical SMT was observed. Pulse pressure increased after cervical SMT. A non-significant decrease in pulse pressure after thoracic SMT was observed. No significant changes in the pulse rate for all interventions. A bigger amount of decrease in heart rate variability for cervical SMT than for thoracic SMT was observed.

Article	Participant characteristics	Design	Intervention	Control	Neurophysiologic outcome parameters	Other outcome parameters	Main outcome
Win, N. N., et al. (2015). Effects of Upper and Lower Cervical Spinal Manipulative Therapy on Blood Pressure and Heart Rate Variability in Volunteers and Patients With Neck Pain: A Randomized Controlled, Cross-Over, Preliminary Study. (49)	N = 20 10 asymptomatic and normotensive subjects, 10 acute neck pain and normotensive subjects Age: Asymptomatic participants 21±1 years, symptomatic participants 20±2 years	Randomised controlled, cross-over, preliminary study	Upper and lower cervical SMT (C1/2, C6/7)	No control. Pre-post comparison.	Heart rate variability, blood pressure, heart rate	Numeric pain scale	Significant decrease in systolic blood pressure following upper cervical SMT in both groups. No other significant changes in the healthy subjects group. Significant decrease of systolic blood pressure in patient's group following lower cervical SMT and a decrease on the numeric pain scale. No significant changes in heart rate and diastolic blood pressure were observed. Upper cervical SMT causes an increase in sympathetic activity Lower cervical SMT causes a decrease of sympathetic activity. Coincident upper and lower cervical SMT causes a decrease of sympathetic activity

Article	Participant characteristics	Design	Intervention	Control	Neurophysiologic outcome parameters	Other outcome parameters	Main outcome
Zhang, J., et al. (2006). Effect of chiropractic care on heart rate variability and pain in a multisite clinical study. (50)	Part 1: N = 539 Healthy volunteers with a history of back pain or head ache, chronic or acute Average age: 46±15 years Part 2: N = 111 Average age: 43±16 years	One group pretest posttest	SMT 71.74% (60.55% diversified manipulation, 9.72% Gonstead techniques, 1.47% upper cervical manipulation) Not SMT 28.25%: (11.19% activator based adjustment, 5.87% Toftness, 5.67% Logan, 1.65% sacrooccipital technique, 5.87% other techniques.)	No control. Pre-post comparison of intervention group.	Electrocardiogram Part 1: Heart rate variability pre- and postthrust. Part 2: Heart rate variability once every week over 4 weeks	Visual analogue scale	After one intervention, pain and heart rate were significantly reduced. After four interventions, pain was significantly reduced whereas heart rate did not change significantly.

H-reflex, T-reflex (11 papers)

Table 6: Overview on the papers to the H-reflex and T-reflex

Article	**Participant characteristics**	**Design**	**Intervention**	**Control**	**Neurophysiologic outcome parameters**	**Other outcome parameters**	**Main outcome**
Boët, C., et al. (2013). High-velocity low-amplitude thrust manipulation of the lumbar spine immediately modifies soleus T reflex in asymptomatic adults. (51)	N = 42 Asymptomatic adults Age: ≥18 years	Randomised controlled pre/post measures experimental design	SMT L4/L5	Sham manipulation	EMG signals of M. soleus bilaterally for T-Reflex amplitude and velocity		Increase in the conduction velocity after SMT, no change after the control intervention. No change of the T-reflex amplitude by neither of the experiments.
Dishman, J. D. and R. Bulbulian (2000). Spinal reflex attenuation associated with spinal manipulation. (52)	N = 17 Healthy volunteers Age 20-43 years	Non-randomised controlled trial	Lumbar SMT	Mobilization without thrust	H-reflex with EMG of M.gastrocnemius: α-motoneuronal activity measured by the amplitude of the N. tibialis Hoffmann reflex at M. gastrocnemius		α-motoneuronal excitability is transiently (for 30s) attenuated by SMT and spinal mobilization, measured by the H-reflex amplitude.
Dishman, J. D. and R. Bulbulian (2001). Comparison of effects of spinal manipulation and massage on motoneuron excitability. (9)	N = 15 Asymptomatic volunteers Age: 20-40 years	Randomised controlled trial	Lumbar SMT	Lumbosacral and limb massage Or Control group	H-reflex of N.tibialis for α-motoneuronal activity		α-motoneuronal excitability is attenuated immediately by SMT. No reduction by massage or in the control group.

Article	Participant characteristics	Design	Intervention	Control	Neurophysiologic outcome parameters	Other outcome parameters	Main outcome
Dishman, J. D., et al. (2002). Comparison of tibial nerve H-reflex excitability after cervical and lumbar spine manipulation. (8)	N = 36 Healthy human subjects without LBP Age: 27.3±4.08 years	One group pretest-posttest	Cervical SMT and Lumbar SMT	No control. Pre-post comparison of intervention group	H-reflex of N.tibialis measured at M.gastrocnemius, α-motoneuronal excitability		Lumbar SMT attenuated lumbar α-motoneuronal activity (amplitude of H-reflex) and transiently suppressed motoneuronal excitability. Cervical SMT had no effect on those distal measurements.
Dishman, J. D. and J. Burke (2003). Spinal reflex excitability changes after cervical and lumbar spinal manipulation: a comparative study. (53)	N = 9 Asymptomatic, healthy volunteers Age: -	One group pretest-posttest	C5/C6 SMT or L5/S1 SMT (change after 48 hours)	No control. Pre-post comparison of intervention group	H-reflex of N.tibialis, H-reflex of N.medianus		Both interventions produced an attenuation of motoneuron excitability. α-motoneuronal activity is attenuated more by lumbar SMT than by cervical SMT.
Dishman, J. D., et al. (2005). Evaluation of the effect of postural perturbation on motoneuronal activity following various methods of lumbar spinal manipulation. (54)	N = 34 and 20 Asymptomatic young healthy volunteers Age: -	One group pretest-posttest	<u>Experiment 1</u> 1.1a) Assisted joint manipulation or 1.2a) Unassisted joint manipulation <u>Experiment 2</u> 2a) L5/S1 side-posture SMT	<u>Experiment 1:</u> 1.1b) Assisted joint preload force Or 1.2b) Unassisted joint preload force <u>Experiment 2:</u> 2b) Side-posture positioning	M.gastrocnemius H-reflex and M(max) to calculate H/M(max) ratios.		<u>Experiment 1</u> H/M(max) ratio attenuation of 1.1a) 18.2% 1.1b) 8.5% 1.2a) 9.5% 1.2b) 7.5% <u>Experiment 2</u> H/M(max) ratio attenuation of 2a) 28.4% 2b) 15.3% Attenuation was significantly greater after SMT in experiment 2.

Article	Participant characteristics	Design	Intervention	Control	Neurophysiologic outcome parameters	Other outcome parameters	Main outcome
Dishman, J. D., et al. (2012). Understanding inhibitory mechanisms of lumbar spinal manipulation using H-reflex and F-wave responses: a methodological approach. (55)	N = 66 Healthy volunteers Age: 20-50 years	Randomised controlled trial	L5/S1 SMT	L5/S1 joint pre-loading procedure Or Control condition	N. tibialis: H-reflex, F-wave, H(max)/M(max)		F-waves and M-waves did not change significantly after mechanical intervention on the spine. H(max)/M(max) ratios decreased until 10s after the intervention. The biggest change was after SMT, a smaller one after joint preloading. No decrease of the ratio after the control intervention.
Floman, Y., et al. (1997). Spinal manipulation results in immediate H-reflex changes in patients with unilateral disc herniation. (56)	N = 24 Patients with unilateral disc herniation at L5/S1 level. Predominant sciatica, no motor or sphincteric involvement. Visible on CT or MRI. Age: 20-50 years	One group pretest-posttest	Single-session lumbar SMT in a side-lying position	No control group. Pre-post comparison of intervention group and comparison between the two sides.	M.gastrosoleus H-reflex		No significant changes in H-reflex latency, but a trend towards shorter latencies.
Fryer, G. and A. J. Pearce (2012). The effect of lumbosacral manipulation on corticospinal and spinal reflex excitability on asymptomatic participants. (7)	N = 14 asymptomatic volunteers Mean age: 23±5.4 years	Randomised, controlled crossover design	L5/S1 SMT bilaterally	Lateral recumbent position for 45 s without truncal torque or manual contact	H-reflex of M. gastrocnemius via N.tibialis	Motor-evoked potential (MEP), MEP/M-wave ratio	H-reflex reduction after SMT.

Article	Participant characteristics	Design	Intervention	Control	Neurophysiologic outcome parameters	Other outcome parameters	Main outcome
Groisman, S., et al. (2014). H-reflex responses to high-velocity low-amplitude manipulation in asymptomatic adults. (57)	N = 19 Asymptomatic adults Age: 30.8±5.5 years	Prospective controlled experimental study with pre and post-intervention measurements	SMT of L5/S1	L5/S1 control intervention before SMT	Motoneuron excitability, H-reflex		H-reflex alteration was in 6/19 significant after SMT with 20% decrease. In 13/19 patients the H-reflex was not significantly changed.
Niazi, I. K., et al. (2015). "Changes in H-reflex and V-waves following spinal manipulation." (58)	Study 1: N = 10 Age 27.6 ±5.4 years Study 2: N = 8 Age 32.6 ± 9.3 years Evidence of spinal dysfunction without known contraindications for SMT.	Randomised cross-over	Spine or sacroiliac SMT Study 2: twice	Passive and active movements of head, spine and body, manipulation setup position Study 2: twice	H-reflex of M. soleus via N.tibialis Study 2: -	M.soleus: V-wave, M-wave, maximum voluntary contraction in surface-EMG of the plantar flexors, H-reflex threshold Study 2: only force was measured	Increased maximum voluntary contraction and force following SMT. Increased V/M(max) ratios and reduced H-reflex thresholds (motoneuron activation) after SMT. For the control intervention it was opposite.

5.3. Main Results

Table 7: Main Results

Part of nervous system	Number of studies	Main findings
Afferent nervous system	13	**Brain activity:** increase in inferior prefrontal cortex, anterior cingulated cortex, temporal gyrus. Decrease in cerebellar vermis, visual association cortex, insular cortex. **Cortical component of SSEP**: decrease. **Repositioning sense**: improves. **Proprioception and postural sway**: ambiguous results. **Sensibility to thermal stimuli**: no change.
Efferent nervous system	7	Ambiguous results.
Sympathetic and parasympathetic nervous system	22	**Skin conductance**: increase. **Systolic blood pressure**: ambiguous results. Blood levels of **cortisol, neurotensin, oxytocin, β-endorphin**: increase. Blood levels of **norepinephrine and epinephrine**: no effect. Blood level of **salivary amylase**: decrease. **Pupil diameter**: no effect. **Heart rate variability**: ambiguous results.
H-reflex, T-reflex	11	**H-reflex**: attenuation. **T-reflex**: no effect.

6. Discussion

6.1. Summary of results

Afferent nervous system

All studies that investigated the effect of SMT on brain activity, all reported a significant effect of SMT with an increased activity in the inferior prefrontal cortex, the anterior cingulated cortex and the temporal gyrus and a decreased activity in the cerebellar vermis, the visual association cortex and the insular cortex. However, one study found the observed effect also after mobilization and therapeutic touch. Three studies investigated the effect of SMT on SSEP. All found a decrease of the cortical component after cervical SMT, while control interventions lead to an increase or no change. Five studies investigated the effect on repositioning sense, proprioception and postural sway. Two studies found a better joint repositioning sense after SMT and results for proprioception and postural sway were ambiguous. As for the effect of SMT on the sensibility to thermal stimuli, there was one study that did not find any change.

Efferent nervous system

Seven studies investigated the effect on MEP, measured at different sites. Two found no effect after a single SMT intervention. In contrast, two studies reported an increase, one a decrease, one did not make a statement and one was ambiguous.

Sympathetic and parasympathetic nervous system

Of the five studies that investigated the effect on skin conductance, three found an increase that was bigger following SMT than a control intervention. One study found a decrease following SMT to T1-L3. One found no change and one had ambiguous results. Seven studies investigated the changes in blood pressure. Three studies found a decrease in systolic blood pressure following cervical SMT and two studies reported a decrease in diastolic blood pressure. However, three studies did not find any change in blood pressure after cervical or thoracic SMT. Furthermore, five single studies found an increase in blood levels of cortisol, neurotensin, oxytocin and β-endorphin after SMT, no effect on norepinephrine and epinephrine and a decrease in salivary amylase. Decrease of cortisol and β-endorphin levels after the control intervention was observed. One study found that pupil diameters did not significantly change following SMT. The results of the eight studies on the effect of SMT on heart rate variability were ambiguous. Three studies found no change at all. Two of the studies claimed an increase in low frequency components and a decrease in high frequency components. One study found an increase in the high frequency components. One study stated a decrease in the heart rate variability which was higher after cervical than after thoracic SMT. One further study found that the heart rate variability was changed after one single SMT, but not after four treatments.

H- and T-reflex

Seven of 10 studies on the H-reflex response found an attenuation after SMT. Most of the studies found that the attenuation after SMT was bigger than after the control intervention. Two studies reported no significant change while one study found an increase.

The only study that investigated the effect of SMT on the T-reflex, found no effect on the amplitude, but an increase in nerve conduction velocity.

6.2. Strengths and limitations

The strengths of this study were that different levels of the nervous system were taken into account. So far, most reviews focused on one single aspect. However, for informing the clinicians, it is important to give insight into more than one aspect. Furthermore, a professional literature research was performed and clearly defined inclusion and exclusion criteria were used. The list of studies resulting from this thesis that includes important study characteristics with their respective results can serve as an overview for clinicians. The fact that animal studies were excluded from this review can be seen as strength as it is difficult to transfer neurophysiological science from animals to humans. However, it is also a limitation as some neurophysiologic techniques are, for ethical reasons, only applied to animals. Thus, such findings are not included in this overview. Another limitation was that this review, although it focuses on different parts of the nervous system, still only gives a partial impression on the total effects of SMT and its impact on muscles and joints was not addressed.

6.3. Importance of the study

SMT is the main treatment technique used by chiropractors, as it is shown to be an effective method to reduce back pain (59-63). Therefore it is important to understand the underlying mechanics of its effect in greater detail. As for clinicians, this knowledge forms the background to inform patients and the referring physicians of expected results from SMT. Results from this study may also help to foresee specific side effects of SMT. For scientific purposes it is important to detect gaps in this knowledge that should be filled by further research studies. For the afferent system for example, contact heat evoked potentials (CHEPS) could be a possibility to observe sensibility changes after SMT. As for the sympathetic and parasympathetic nervous system, MEP from the N.pudendus and from the palm of the hand could be an option to have comparable results between patients. Furthermore, it would be of interest to focus on the long term changes that are induced by SMT as most studies focused on single interventions with short follow-up periods. Lastly, future studies on SMT should focus on the treatment of a single segment, which is clearly defined as this would improve the comparability of the results.

6.4. Conclusion

In literature, many studies show a beneficial effect of SMT on pain intensity. The results of the present review suggest that this effect could be based on changes in the afferent nervous system, as all studies on changes in brain activity and somatosensory evoked potentials after SMT reported relevant changes. The results of the effects on SMT on the efferent nervous system were inconclusive. SMT seems to affect the sympathetic nervous system by changing peripheral blood flow. Furthermore, effects of SMT on blood levels of some hormones and on skin conductance were observed. H-reflexes showed attenuation after SMT. Future studies should apply SMT to single, well-defined segments and focus not only on the effects of single SMT, but also on its long term effects on the nervous system.

6.5. Acknowledgements

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